What are the most pressing challenges in psychiatry clinical trials? How are scientists addressing them?

In conversation with... Leslie Citrome, MD, MPH

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Q **Dr. Opler : Before we begin, could you tell us about yourself, how you got into clinical research and psychiatry, and why this field matters so much to you?**

A **Dr. Citrome** : After graduating from my residency program, I took a clinical job at a VA hospital running the psychiatric intensive care unit; I then moved into an administrative position at a state hospital. But shortly thereafter, I realized administration wasn't for me: I wanted to do something more in the research realm.

I joined the staff at the Nathan Kline Institute for Psychiatric Research operated by the New York State Office of Mental Health. I was hired to start up a unit; clinically, it was very similar to my prior work, but with a twist. This unit would be focused on research and evaluation of the chronically mentally ill who would find themselves admitted to a state hospital–in this case Rockland Psychiatric Center. My mentor there, Dr. Jan Volavka, taught me the ropes–how to implement a clinical trial and ultimately how to design and interpret them. I learned a tremendous amount from him. I owe him a lot–I owe my career to Dr. Volavka.

During the nearly 20 years I spent at the Nathan Kline Institute, I learned a lot about the importance of having the right patients in the trial and using the right measures. I became fascinated by the different types of treatments that we could offer our patients–patients with schizophrenia in particular.

Q **Dr. Opler : To begin, what do you see as the top challenges in clinical trials' methodologies and the conduct of trials in psychiatry?**

A **Dr. Citrome** : Well, the top three challenges are really quite profound.

One is heterogeneity. When we say someone has schizophrenia, it's

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Leslie Citrome, MD, MPH, *a member of WCG's Scientific Leadership Team, shared his insights during a recent conversation with Mark Opler, MD, PhD, chief research officer at WCG-MedAvante-ProPhase. Dr. Citrome has a private practice and is clinical professor of psychiatry and behavioral sciences at New York Medical College in Valhalla.*

The interview has been edited for clarity and length.

not really all that precise. It's hard to assemble a group of people with a similar disease, especially when we don't know the pathophysiology. What we call schizophrenia is probably schizophrenias. I wish there were a better way to better classify these disorders so we could form more homogeneous groups to study. In the future, perhaps biomarkers would help us assemble groups of patients that are more similar than different. That's our biggest challenge in terms of formulating a clinical trial.

Then there's the actual conduct of the clinical trial, which is also quite challenging. It has changed over the years. When I started out, it was mainly academic medical centers that conducted clinical trials either as part of their own research programs or under contract with pharmaceutical companies to develop new medicines. The academic medical center has specific priorities in advancing knowledge and not necessarily addressing the financial bottom line. Of course, it was nice to generate income to pay for support staff and soft money to pay for additional research assistants and so on, but it was quite secondary to the scientific mission of the center. But that has changed.

Now the locus of where clinical trials are conducted for drug development is primarily in commercial endeavors--commercial operations whose main goal is to turn a profit. That's not a bad thing, of course, and there are commercial sites there that do an excellent, high-quality job in the recruitment and conduct of a study, but I also have some concerns. If they are overextended and are spending a lot of time in diverse clinical trials, they may not develop the internal expertise to address the entity that I want to study myself.

If I'm running a trial on schizophrenia across many different sites, I want those sites to be experienced enough to be able to do the job. The idea of different sites competing for patients makes it difficult to incentivize high-quality recruitment efforts: If sites are competing against each other to recruit as many patients as possible within a short period of time, we're going to have some problems in terms of the patients being recruited. Heterogeneity increases and we're going to have, for example, less ability to detect a signal between our intervention and placebo. That's a major challenge.

Lastly, a challenge that I know is not going to be addressed overnight is the actual design of the clinical trial. What are you going to measure? How are you going to measure that–and how are you going to make that as accurate and valid as possible? Should it be purely a pathophysiological outcome? That's hard to do in our field, in psychiatry, and so we focused on psychopathology rather than pathophysiology, and psychopathology is not always going to address the symptoms that we're going to primarily be caring about in the day-to-day treatment of patients.

So we're looking toward other measures that address functionality, so to speak, and how to choose which will be your primary outcome measure and which will be your secondary outcome measure. Those are big challenges as well. I think we're going to have to think through some of our outcome measures to make studies more clinically relevant to the end-user, which is the clinician.

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Dr. Opler : If you were in the process of starting up a clinical trial today, what are the three things would be worried about? What are the top three concerns or fears or challenges you think someone leading the study day-to-day needs to be focused on?

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Dr. Citrome : Well, my first concern is who's doing the trial? Who am I contracting with to do the trial? Is it a group that is doing lots of different trials across a lot of diverse disease states and so on? How much attention can they pay to my individual? And if they are overextended then I'm probably going to have a rough time getting the numbers of patients that I need from that site, or quality that's high enough that it would be worthwhile. So that would be my first worry, is who am I contracting with and are they able to actually do this study in a conscientious manner and provide data that is useful?

The other concern is the site: What degree of experience does it have in doing the measures? If the site itself is expected to do the primary outcomes measures, then I want to make sure that it can do a reasonable job, a valid job and a quality job–and that it's also amenable to training, follow-up, etc. Centralized grading can obviate some of these issues, but not completely. So that would be my other primary concern.

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Dr. Opler : Moving from our fears to our hopes and thinking now about what's gone well: In the past 12 months, are there any developments that you're particularly excited about? Is there anything you can share with us that's happened over the last year that you feel will have a meaningful impact on the lives of our patients?

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Dr. Citrome : It's really exciting that we're starting to explore different molecules–molecular entities–that have a different mechanism of action. This addresses the heterogeneity challenge. Not everyone is the same, so not all the treatments are going to be useful. For a long time, we've relied on drugs that are very similar rather than have any substantial differences, so I'm really excited to see drugs that are being developed that have unique mechanisms of action that may help some of our patients in ways prior medicines simply did not. That's my number one area of enthusiasm right now.

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Dr. Opler : That's very good to hear, but it's clear from what you've said that there's still room improvement and opportunity for advancing the field. Where are the top areas we can make a difference in clinical development? Where do we need to focus our attention to move psychopharmacology forward?

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Dr. Citrome : Well, I think we need to be very mindful about the effect sizes of the interventions we're testing. It's one thing to establish statistical significance over placebo. That's been an obsession over the years, to make sure that you've met your statistically significant threshold, but it really doesn't address the question: "Is this intervention going to be useful in the day-to day-treatment of patients?"

Now we do have a better appreciation of what would be a minimal clinical improvement that we would state upfront that we would want to exceed, and we have better ways of expressing effect sizes that would be easily translatable to the individual clinician. For example, I've been working many years looking at the metric of "number needed to treat" and trying to use that as a way of expressing the usefulness of a medicine that has been demonstrated to be statistically significantly superior to placebo–but how much superior is it? Is it going to be relevant in a day-to-day treatment of patients? So I'm excited to see that there's a better appreciation of this and I think we'll see more of it.

When you listen to the audio recordings or read the transcripts of the Food and Drug Administration Advisory Committee meetings, you'll hear a lot about the actual treatment effect of the intervention being proposed and whether it's significant enough to consider this drug as approvable. This is different than how we used to talk about drugs years ago, and I think pharmaceutical companies are beginning to take notice of this. They are talking more about the importance of effect size in their documents that they prepare for such a meeting; that's interesting and that's going to continue to grow.

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Dr. Opler : Continuing on with predictions, what do we have to look forward to in 2019? Do you think there are going to be any surprises on the horizon?

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Dr. Citrome : I think we're going to see some treatments being approved for entities that have had no treatments thus far. I'm being optimistic here, and it may not be this year or the year after, but certainly within the next five years I think we'll see treatments for psychosis associated with dementia. I think we'll see alternatives to stimulants for disorders such as binge eating disorder. I think we'll see some novel antipsychotics that principally work not by blocking dopamine detour centers but through some other mechanism; they appear to do a fine job in reducing hallucinations and delusions without some of the debilitating side effects that some of our current medicines carry. So I think there's a lot to look forward to, but it may not be overnight.

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Interviewee

Leslie Citrome, MD, MPH is an Adjunct Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York. His primary research has centered on psychopharmacologic approaches to schizophrenia, management of treatment-refractory schizophrenia, and the management of aggressive and violent behavior.

Interviewer

Mark Opler, MD, PhD, serves as Chief Research Officer, directing scientific research and development at MedAvante-ProPhase. Dr. Opler was the founder of ProPhase and served as its CEO and Chief Scientific Officer among other positions. He holds the titles of Adjunct Assistant Professor of Psychiatry at New York University and Assistant Professor of Clinical Neuroscience at Columbia University's College of Physicians and Surgeons.